I. SUMMARY

Inorganic chloramines are alternate disinfectants that are rapidly formed when free chlorine is added to water containing ammonia. To achieve the desired chloramine concentration, chlorine may also be intentionally added to the already naturally occurring ammonia in the water source. Under the usual conditions of water and wastewater chlorination, monochloramine is the principal chloramine encountered. In the event of excess hypochlorite or at lower pH, ammonia can be di- and trichlorinated and organic amines can be dichlorinated. Comparatively little is known about the physical properties of pure dichloramine because it is not stable and is difficult to synthesize. Trichloramine is formed in acidic solutions where chlorine concentrations are much greater than those of ammonia. This document will deal primarily with inorganic chloramines; however, where data are limited or not available various chlorinated amino compounds (including organic chloramines) will be provided as supplemental information.

Inorganic dichloramine is unstable and decomposes to nitrogen, hypochlorous acid and other products. This reaction accounts to a large extent for the breakpoint reaction seen in water chlorination. Inorganic monochloramine is a much poorer disinfectant than hypochlorous acid, and it reacts slowly with organic amino nitrogen compounds to produce organic N-chloramines, which are even poorer disinfectants.

Conventional methods of monochloramine analysis have led to confusion in the use of the term "chloramines." The term has been used to describe many compounds in

complex mixtures that oxidize iodide to iodine, the amount of which is subsequently determined by colorimetric or amperiometric analysis. Organic N-chloramines and N-chloramides respond similarly to monochloramine; however, they are poor disinfectants compared with inorganic chloramine. From a public health viewpoint, these ambiguities can present serious problems since the disinfecting capabilities of waters that contain organic N-chloramines could be overestimated. Improved analytical methods are needed for the determination of organic and inorganic N-chloramines in chlorinated waters. For the purpose of this document, the term "chloramines" will refer to a combination of inorganic mono-, di- or trichloramines unless otherwise stated.

Human exposure to chloramines is through ingestion of chlorinated water containing ammonia or chloraminated water. Chloramination is a technique that is being adopted by many communities to avoid formation of trihalomethanes on water disinfection. Organic chloramines have been shown to form upon chlorination of stomach fluid *in vitro*. However, the significance of their formation on ingestion of chlorinated water is not clear.

Information on the absorption of inorganic chloramines is extremely limited. In one study an absorption rate constant was calculated for monochloramine at 0.278 mg/hour (after 8 hours) with an absorption half-life of 2.5 hours after a single oral dose of ~4.6 mg/kg/day was administered to Sprague-Dawley rats. After 48 hours, the rate constant was 0.018 mg/hour. Absorption rates with respect to various dosage media and different routes of exposure were not available.

The distribution of radiolabeled chlorine in the subfractions of rat liver homogenates in organs, tissues, and fluids was similar (120 hours) after oral administration of either $^{36}Cl^-$ (200 mg/L as $Na^{36}Cl$) or $NH_2^{36}Cl$ (370 mg/L $NH_2^{36}Cl$). Plasma contained the highest concentrations of 36Cl radioactivity for $NH_2^{36}Cl$ followed by whole blood, skin, testes, packed cells, bone marrow, kidney, lung, stomach, thyroid, thymus, duodenum, spleen, carcass, liver, ileum and fat. The major metabolite of $NH_2^{36}Cl$ was $^{36}Cl^-$.

Information on the metabolism of chloramines is also extremely limited. One experiment indicated that chloramines are transformed to the chloride moiety and eliminated primarily in this form.

Chloramines are eliminated primarily through the urine. During the first 24 hours after a single dose of $NH_2^{36}Cl$ (1.1 mg/animal) to Sprague-Dawley rats, only 0.40 and 0.08% of the total dose was eliminated in the urine and feces, respectively. At the end of 120 hours, 25.15 and 1.98% of the dose was eliminated through the urine and feces, respectively. By comparison 16.1 and 0.92% of $^{36}Cl^-$ radiolabel (200 mg/L as $Na^{36}Cl$) was eliminated in the urine and feces, respectively, in the first 24 hours. Over twice as much of the $^{36}Cl^-$ radiolabel was eliminated over a 120-hour period. The major difference between the $NH_2^{36}Cl$ and $^{36}Cl^-$ studies was in the total amount of label excreted over the test period.

Several short-term studies showed no observed adverse hematologic effects in mice, rats and monkeys. In A/J mice administered chloramine solutions between 2.5 and 200 mg/L (pH 8.9) for 30 days, the only observable effect was a slight increase in hematocrit. In another study of similar duration (45 days) rats treated with 10, 50 or 100 mg/L monochloramine experienced a decrease in the amount of methemoglobin present in the blood, the opposite of what was expected. Monochloramine in drinking water for 6 weeks at 100 mg/L had no detectable effects on 18 hematologic tests of 12 African Green monkeys.

In a 12-month study using Sprague-Dawley rats administered 1, 10 and 100 mg/L monochloramine, glutathione levels, red blood cell count and hematocrit were found to be decreased at sporadic intervals. However, there was a lack of dose- and time-dependent response in the results. Plasma thyroxine levels were significantly decreased and cholesterol elevated in pigeons administered 15 mg/L monochloramine for 3 months.

Rats and mice were administered monochloramine in drinking water at concentrations of 0, 25, 50, 100, 200 or 400 ppm (0, 25, 50, 100, 200 or 400 mg/L) for 91 days. Decreased body weight gain and liver damage were observed at 200 and 400 mg/L in rats and 100, 200 and 400 mg/L in mice. Histopathologic observation revealed mild to moderate cytologic alteration in the liver of male mice administered 200 and 400 mg/L chloramines. Chronic liver inflammatory changes occurred at 100, 200 and 400 mg/L in female mice and to a lesser extent in male mice at the 100 ppm level. Microscopic

examination of rat tissues at the 400 mg/L level did not reveal any treatment-related lesions. The investigators suggested a NOEL of 50 mg/L or ~8.3 mg/kg/day monochloramine based on chronic liver inflammatory changes in mice.

In a 90-day study, male and female Sprague-Dawley rats were administered monochloramine in drinking water at concentrations of 0, 25, 50, 100 and 200 mg/L. At 200 mg/L the average weight gain was 51% of controls. There were also reductions in organ weights (absolute, relative or both) at the high dose level. The authors identified the 100 mg/L dose as the NOAEL.

B6C3F1 mice were administered monochloramine in their drinking water for 90 days at 0, 12.5, 25, 50, 100 and 200 mg/L. There were weight gain reductions, and reductions in absolute and relative organ weights at the 100 and 200 mg/L dose levels. Based on these reductions the authors identified a NOAEL of 50 mg/L.

In a 2-year study, F344/N rats and B6C3F1 mice were administered 0, 50, 100 and 200 ppm monochloramine in their drinking water. There was a decrease in mean body weight in high-dose rats. The high-dose group had decreases in organ weights and increases in organ-to-body weight ratios at 14- or 66-week evaluations. There was also a dose-related decrease in mean body weights of dosed male and female mice throughout the study. There were decreases in organ weights and increases in organ-to-body weight ratios observed in high-dose mice at 15- or 66-week evaluations.

Monochloramine was not teratogenic in mature female Sprague-Dawley rats exposed to 1, 10 or 100 mg/L in drinking water, nor did 40, 100 and 200 mg/L solutions induce sperm-head anomalies in B6C3F1 mice. In addition, no significant differences in fertility, viability, litter size, day of eye opening or day of vaginal patency were observed between control and exposed Long-Evans rats given $\geq$10 mg/kg chloramines. There were no alterations in sperm count, direct progressive sperm movement, percent mobility or sperm morphologic characteristics.

Results on the mutagenicity of chloramines are inconclusive. Monochloramine has been found to be marginally mutagenic in *Bacillus subtilis* and in *Vicia faba* plant seeds. In *Salmonella typhimurium* (TA97, TA100 and TA102), chloramines (40 um) marginally increased the number of revertant colonies over untreated controls. It was responsible for cellular hypertrophy, increased mitotic figures and bizarre chromatin patterns in B6C3F1 mice exposed to 200 and 400 mg/L in drinking water. In another study, monochloramine at 40, 100 and 200 mg/L did not induce chromosomal aberrations or micronuclei in bone marrow of CD-1 mice.

The organic chloramine, N-chloropiperidine, was found to be marginally mutagenic in the reverse mutation plate incorporation assay (Ames test). It was cytotoxic and cytostatic in CHO cells and produced chromosomal aberrations, the frequency of which was proportional to the concentration of the compound. It produced SCEs in CHO cells, but not in baby hamster kidney cells. The analogous chloramine, N-chlorodiethylamine, was more toxic but nonmutagenic. When the synthetic N-Cl compound chloramine T

(sodium p-toluene-sulfonyl chloramide) was tested, SCEs were significantly increased in a dose-dependent manner in CHO cells.

Organic concentrates of water treated with monochloramine produced papillomas, squamous cell carcinomas and lung adenomas in SENCAR mice. These data are inadequate, however, to assess the carcinogenic potential of monochloramine. In a 2-year study using male and female F344 rats and B6C3F1 mice, monochloramine was administered in drinking water at 0, 50, 100 and 200 ppm. Equivocal evidence of carcinogenic activity was found in female rats because of the slightly increased incidence of mononuclear cell leukemia. There was no evidence of carcinogenic activity in male rats or female or male mice, which was attributed to chloraminated drinking water.

Information concerning human exposure to chloramines is extremely limited. In humans, acute exposure by inhalation of chloramine fumes has been observed after mixing 4-5% solutions of ammonia and sodium hypochlorite in a small room. Pneumonitis resulted, but no permanent pulmonary damage occurred. Very few experimental studies have been conducted. Individuals ingesting levels of chloramines between 0.01 and 24.0 mg/L for 1 day or 5 mg/L for 12 weeks showed no hematologic or detrimental physiologic responses resulting from chloramine ingestion.

There are no epidemiologic studies that have been designed to address specifically the potential adverse effects of exposure to chloramines on human health. One study was conducted to see if there was a difference in cancer mortality among

communities using chlorine compared with communities using chloramine for disinfection. This study was not designed to assess adverse effects from exposure to chloramine but rather to consider the chloramine-exposed participants as controls.

Chloramines appear to be produced by normal human neutrophils as part of their bactericidal action. Chloramines are believed to exert their effects by interfering with enzymatic reactions. Monochloramine oxidizes and denatures hemoglobin and inhibits the hexose monophosphate shunt. It also causes strand-breaks in DNA.

Lack of sufficient data preclude the derivation of a 1-day HA for chloramines. It is recommended that the 10-day HA of 1 mg/L be adopted as the 1-day HA. The 10-day HA was derived from a drinking water study using African Green monkeys. The 10-day HA for a 10 kg child is 1 mg/L based on the absence of hematologic effects. The longer-term HAs for a 10 kg child and 70 kg adult are 1 and 4 mg/L, respectively. These HAs are based on a NOAEL for body and organ weight changes in rats exposed to chloramines in drinking water. The DWEL of 4 mg/L is derived from a proposed RfD of 0.1 mg/kg/day from a NOAEL in a chronic drinking water study using rats, based on absence of decreased organ weight changes.

There was one 2-year bioassay with equivocal evidence of carcinogenic activity in female rats. The CRAVE Work Group verified (12/02/92) a classification for monochloramine of group D, not classifiable as to human carcinogenicity, meaning that there is inadequate human and animal evidence of carcinogenicity.